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Rationale and study design of the Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker MEasuring arterial sTiffness in the eldERly (PARAMETER) study

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ABSTRACT

Background: Hypertension in elderly people is characterised by elevated systolic blood pressure (SBP) and increased pulse pressure (PP), which indicate large artery ageing and stiffness. LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), is currently being developed for the treatment of hypertension and heart failure. The Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker MEasuring arterial sTiffness in the eldERly (PARAMETER) study will assess the efficacy of LCZ696 versus olmesartan on aortic stiffness and central aortic haemodynamics.

Design and methods: In this 52-week multicentre study, patients with hypertension aged ≥60 years with a mean seated (ms) SBP ≥150–<180mmHg and a PP>60mmHg will be randomised to once-daily LCZ696 200mg or olmesartan 20mg for 4 weeks, followed by a forced-titration to double the initial doses for the next 8 weeks. At 12–24 weeks, if the BP target has not been attained (msSBP <140mmHg and ms diastolic blood pressure <90 mmHg), amlodipine (2.5–5mg) and subsequently hydrochlorothiazide (6.25–25mg) can be added. The primary and secondary endpoints are changes from baseline in central aortic systolic pressure (CASP) and central aortic PP (CAPP) at Week 12, respectively. Other secondary endpoints are the changes in CASP and CAPP at Week 52.

Statistical analysis plan: A sample size of 432 randomised patients is estimated to ensure a power of 90% to assess the superiority of LCZ696 over the olmesartan at Week 12 in the change from baseline of mean CASP, assuming a standard deviation of 19mmHg, the difference of 6.5mmHg and a 15% dropout rate. The primary variable will be analysed using a two-way analysis of covariance.

Progress and implications: The study was initiated in December 2012 and final results are expected in 2015. The results of this study will impact the design of future phase III studies assessing cardiovascular protection.

Clinical trials identifier: EUDract number 2012-002899-14 and ClinicalTrials.gov NCT01692301.

Key words: arterial stiffness, central aortic systolic pressure, isolated systolic hypertension, pulse pressure, LCZ696, elderly

Strengths and Weaknesses of this Study

Strengths:

- This is a randomized controlled trial of a new class of drug therapy (angiotensin receptor neprilysin inhibitor – ARNI) for hypertension versus a comparator that blocks only the angiotensin receptor – this will inform on the added value of neprilysin inhibition in the context of systolic hypertension;
- The study incorporates a detailed clinical experimental medicine mechanistic study that will interrogate the actions of this new drug class on vascular haemodynamics and function;
- The study evaluates the a novel treatment approach for a major unmet clinical need, i.e. systolic hypertension

Weaknesses

- The study has inadequate statistical power to assess the impact of the interventions on major clinical outcomes beyond blood pressure and vascular haemodynamics and function.

INTRODUCTION

Hypertension accounts for 9.4 million cardiovascular (CV) deaths annually worldwide and is affecting more than two-thirds of people aged ≥65 years, an age group that is growing globally.[1,2] The treatment of hypertension has been shown to reduce the risk of morbidity and mortality associated with elevated blood pressure (BP) including stroke, ischaemic heart disease, heart failure, chronic kidney disease and possibly cognitive decline.[3] Despite the availability of multiple drug classes with different mechanisms of action, hypertension, especially systolic blood pressure (SBP), remains inadequately controlled.[4]

The SBP usually increases from childhood throughout the life, while diastolic BP (DBP) remains relatively constant or decreases beyond 50 to 60 years of age. This indicates that the worldwide burden of hypertension beyond 50 to 60 years is mostly due to systolic hypertension. Furthermore, the progressive increase in SBP and decrease or no change in DBP widens pulse pressure (PP), and results in the development of isolated systolic hypertension (ISH), which is the predominant form of hypertension in elderly patients. The National Health and Nutrition Examination Survey (NHANES) III reported that the prevalence of ISH was 87% in elderly patients with hypertension.[5] Furthermore, the Framingham Heart Study (FHS) reported almost a 90% lifetime risk of developing ISH in normotensive people reaching the age of 65 years and who survived for another 20 to 25 years.[6]

The changing patterns of BP throughout the life reflect different pathologies. In the young, hypertension is predominantly due to an increased DBP and mean arterial pressure (MAP), as a result of a relative increase in cardiac output and/or increased peripheral vascular resistance.[7] On the other hand, advancing age, beyond mid-life, is associated with an increased stiffness of large elastic arteries, especially the aorta. Arterial stiffening adversely affects the characteristic impedance of the aorta, requiring more cardiac work and raising SBP as more stroke volume is delivered during systole owing to the increased pulse wave velocity (PWV). DBP also decreases due to less elastic recoil leading to reduced flow, thus increasing PP independent of any changes in MAP. PWV been shown to be an independent predictor of CV outcomes, including mortality,[8] myocardial infarction (MI),[8] stroke,[8] atrial fibrillation,[9] cognitive decline[10] and renal dysfunction[11] and more specifically aortic PWV

(aPWV), a robust measure of aortic arterial stiffness, has been shown to predict the adverse CV outcomes.[7]

Another consequence of arterial ageing and stiffening is that the amplification of SBP and PP from the aortic root to the peripheral arteries diminishes. In a healthy arterial system, central aortic systolic pressure (CASP) and PP are amplified as they move towards the periphery, such that the measured brachial systolic pressure is typically around 10 mm Hg higher than the corresponding aortic root pressure[12]. With ageing, this amplification is reduced because of the increased PWV and the increase in the early wave reflection resulting in the measured brachial SBP and PP becoming closer to the corresponding aortic root pressures. Some studies have suggested that central pressures may have a closer correlation than peripheral BP with end organ damage[13-15] and CV risk,[15] such as extent of coronary atherosclerosis, carotid intima-media thickness, left ventricular hypertrophy, and left ventricular diastolic function.[14,16,17]

These observations raise the intriguing question as to whether treatments used to lower blood pressure could differentially affect aortic relative to brachial pressures and also arterial stiffness per se. It has been demonstrated that BP-lowering drugs can have marked differential effects on central aortic pressure (CAP) and brachial BP.[18] These effects mimic a functional anti-ageing effect in terms of their impact on wave-form morphology, and greater reduction in central pressures relative to brachial pressures. Intriguingly, the beta-blockers, a drug class which was least effective at lowering aortic pressure also appeared to be the least effective class at reducing the risk of stroke in elderly patients.[18] This supports the concept that the more effective lowering of aortic relative to brachial pressure may be clinically important.

Despite the findings cited above, controlling SBP remains the most important unmet need in the clinical management of hypertension. The rise in SBP and PP with ageing appears to be strongly related to arterial stiffening and increased impedance to flow through a stiff aorta. This suggests that the treatments targeting aortic stiffening and reducing characteristic impedance would be effective particularly at reducing systolic pressure. Early proof of this concept came from the studies with omapatrilat, a vasopeptidase inhibitor that simultaneously inhibits neprilysin and angiotensin-converting enzyme (ACE). Neprilysin

inhibition enhances natriuretic peptide (NP) levels by blocking their degradation. NP has vasodilating actions, which could reduce aortic stiffness, improve characteristic impedance and thereby reduce SBP and PP. Studies with omapatrilat show greater improvements in aortic characteristic impedance compared with enalapril, beyond the effects of BP-lowering after 12 weeks of therapy.[19] This benefit on aortic function was also associated with impressive data on SBP and PP lowering in patients with hypertension. Despite this considerable promise, omapatrilat was withdrawn due to safety concerns owing to increased incidences of angio-oedema associated with the ACE-inhibitor component, which was seemingly potentiated by the neprilysin inhibition.

Nevertheless, a proof of concept was established for concomitant inhibition of neprilysin and renin-angiotensin-aldosterone system (RAAS) with the potential to be an attractive treatment strategy to improve aortic haemodynamics. Furthermore, there might be other benefits of neprilysin inhibition in the setting of hypertension, beyond its vasodilator action. Increased NP levels also promote natriuresis and reduce sympathetic tone, together with antiproliferative and antihypertrophic effects, and inhibition of aldosterone secretion.[20] Alongside, suppression of RAAS would be complementary to neprilysin inhibition, which attenuates vasoconstriction, reduces sodium and water retention and also inhibits the development of CV hypertrophy and adverse re-modelling.

Recently LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), has been developed. LCZ696 delivers systemic exposure to a neprilysin inhibitor prodrug, AHU377 (which rapidly converts into active LBQ657), and an angiotensin receptor blocker (ARB), valsartan. LCZ696 at 100, 200 and 400 mg once daily, in patients with mild-to-moderate essential hypertension, resulted in greater BP reductions than corresponding doses of valsartan alone (160 and 320 mg) and was well tolerated.[21] LCZ696 compared with valsartan was effective especially at reducing brachial SBP and PP. Furthermore, in patients with heart failure with preserved ejection fraction, LCZ696 has shown to reduce N-terminal-pro B-type natriuretic peptide (NT-proBNP), a biomarker of left ventricular (LV) wall stress, to a greater extent than valsartan alone at 12 weeks and was well tolerated.[22]

Thus, the big challenge in hypertension treatment is to reduce the SBP, and the available evidence suggests that this could be achieved by improving the haemodynamic performance

of the ageing aorta. The Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker MEasuring arterial sTiffness in the eldERly (PARAMETER) study is designed to compare the effect of LCZ696 with olmesartan, an ARB, on CASP, other measures of central aortic haemodynamics and arterial stiffness, and ambulatory blood pressures in elderly patients with an elevated brachial SBP and a widened PP. The widened PP was chosen as an entry criteria as being indicative of aortic stiffening and advanced aortic ageing. The objective is to determine whether the ARNI LCZ696 can reverse some of the effects of arterial ageing in elderly patients with systolic hypertension, and thereby improve aortic pressures and haemodynamics. The study was initiated in December 2012 and the final results are expected in 2015. This manuscript describes the design, objectives and pre-specified analysis plan for the PARAMETER study.

METHODS

Study design

The PARAMETER study is a 52-week, multicentre, randomised, double-blind, active-controlled, parallel-group study, involving 51 centres from 13 countries (Europe 47%, South America 14%, Asia 19% and US 20% — see online supplement for list of local investigators and participating centres). The study includes a screening period, a placebo run-in, and an initial double-blind treatment period of 12 weeks with LCZ696 monotherapy, followed by a double-blind extension of 40 weeks, during which add-on therapy is allowed to reach the BP treatment goal. Patients will be randomised to receive either once-daily LCZ696 200 mg or olmesartan 20 mg for 4 weeks, followed by a forced-titration to double the initial doses for the next 8 weeks. After 12 weeks, patients with uncontrolled BP (mean sitting [ms] SBP >140 mm Hg and/or msDBP >90 mm Hg) will be prescribed amlodipine (2.5–5 mg) and then hydrochlorothiazide (6.25–25 mg) as needed, at an interval of 4 weeks up to Week 24 (Figure 1). This study has been approved by all relevant ethics committees. The study is registered as EUDract number 2012-002899-14 and on ClinicalTrials.gov under the code NCT01692301.

Study participants

Elderly patients (aged ≥60 years) with essential hypertension (either untreated or treated with antihypertensive agents) and patients who have msSBP ≥150 mm Hg and <180 mm Hg at randomisation are eligible for inclusion in the study. Untreated patients (if they are newly diagnosed or have not been treated with antihypertensive drugs for the 4 weeks prior to screening) must have msSBP ≥150 mm Hg and <180 mm Hg at screening and randomisation, whereas patients who have been treated with antihypertensive agents 4 weeks prior to screening must have msSBP ≥140 mm Hg and <180 mm Hg after 1 or 2 weeks of washout/placebo run-in and ≥150 mm Hg and <180 mm Hg at randomisation. All patients must have a PP>60 mm Hg at randomisation. Patients with malignant or severe hypertension, secondary causes of hypertension, history of atrial fibrillation or atrial flutter during the 3 months prior to screening, or active atrial fibrillation or atrial flutter on electrocardiogram, history of CV disease (e.g., myocardial infarction) during 12 months prior to screening, and

evidence of severe renal impairment (e.g., estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) are excluded – boxes 1 and 2 summarise the inclusion and exclusion criteria, respectively. Patients have to provide a written informed consent before starting any study-related procedures.

The study objectives and endpoints

The primary objective of the study is to demonstrate the superiority of a LCZ696-based treatment regimen over an olmesartan-based treatment regimen in reducing mean CASP after 12 weeks of treatment. Superiority testing is also planned for the key secondary efficacy assessment, i.e. the reduction in mean central aortic PP (CAPP) after 12 weeks of treatment, and other secondary efficacy assessments such as mean CASP and CAPP after 52 weeks of treatment. Mean aPWV, msSBP, msDBP, msPP, mean ambulatory (ma) BP, maPP, and MAP will also be measured after 12 and 52 weeks of treatment.

Exploratory assessments comparing the two treatments after 12 and 52 weeks of treatment include pulse wave analysis (PWA) variables such as augmentation index (AIx), augmentation pressure, PP amplification ratio, duration of left ventricle (LV) ejection, and time to wave reflection; reduction in ma central (mac) BP, macMAP, and macPP; plasma biomarkers including NT-proBNP and urinary cyclic guanosine monophosphate (cGMP)/creatinine ratio and other biomarkers related to hypertension.

Haemodynamic measurements

The SphygmoCor X-CEL System (AtCor Medical, Sydney, Australia) is being used to non-invasively derive the ascending aortic pressure waveform from the brachial waveform using a validated generalised transfer function (GTF).[23] A properly sized BP cuff is linked to a computer and software and the CASP, CAPP, augmentation pressure, and AIx are determined from the analysis of waveform by the system software.

The SphygmoCor X-CEL system also measures the carotid-femoral aPWV, as the speed of the arterial pressure waveform as it travels through the descending aorta to the femoral artery, which is detected from simultaneously measured carotid and femoral arterial pulses. The carotid pulse is detected by applanation tonometry using a high-fidelity pressure

transducer (Millar Instruments, Houston, TX), while the femoral pulse is detected using a partially inflated blood pressure cuff wrapped around the upper thigh. The distance travelled by the pulse wave is captured by making physical measurements on the body surface according to the manufacturer's recommendations. This new brachial cuff-based device with an individualised sub-diastolic cuff pressure has recently been validated against the SphygmoCor device (AtCor Medical) using the classical radial tonometry-based methodology, and provides an operator-independent method to assess systolic pressure and aortic waveform comparable with the existing validated tonometric-based methods.[24] Measurements using SphygmoCor X-CEL system will be performed at baseline, randomisation, Week 12 or at the time of early discontinuation prior to Week 12, Week 52, or at the time of early discontinuation between Week 12 and Week 52.

The 24-hour maCAP and maPWA will be monitored using the oscillometric device, Mobil-O-Graph (IEM, Stolberg, Germany) with integrated ARC solver algorithms (Austrian Institute of Technology, Vienna, Austria). The traditional Mobil-O-Graph ambulatory blood pressure monitoring (ABPM) device has been available for more than a decade and through several product generations.[25-28] The actual blood pressure measuring unit was validated according to the British Hypertension Society (BHS) and the European Society of Hypertension (ESH) recommendations.[25,27] The method equipped with a GTF to derive aortic pressure waveforms[29] is based on brachial readings acquired in the course of the conventional pressure measurement at diastolic level.

During the signal acquisition procedure, the received raw signals are separated into single waves and checked for their plausibility by means of extreme values and corresponding wavelengths using a cross-correlation approach. Poor waveforms are removed from further processing. After applying the GTF to each single waveform, the procedure is repeated. After final coherence verification, the quality judgment of grade '1' states that at least 80% of the waveforms were found to be eligible for further processing, while grades '2' and '3' represent a ≥50% and <50% valid waveforms, respectively.[30]

Surrogates derived by this technique have been validated against solid-state catheter measurements and/or compared with non-invasive readings (e.g., tonometry, echocardiography) for aortic pressures,[30-33] wave reflections,[34] or aPWV.[35,36] However,

potential clinical usefulness has been demonstrated recently.[37-39] Furthermore, feasibility[36] and reproducibility[40] of cuff-based maPWA measurements have been reported. With respect to legal issues, the Mobil-O-Graph maPWA monitor with integrated ARC solver algorithms holds approvals from CE, FDA, and JPAL (amongst others).

Safety assessments

Safety and tolerability assessments include regular monitoring and recording of all adverse events (AEs) and concomitant medications or significant non-drug therapies. Evaluations of routine blood chemistries, blood counts with white cell differential and urine analyses, physical examinations, electrocardiograms (ECGs), and monitoring of vital signs will be performed at regular intervals.

Statistical analysis plan

A sample size of 183 completers per group is targeted, which is calculated based on the primary efficacy variable, change from baseline in mean CASP at 12 weeks, assuming a standard deviation of 19 mm Hg. The sample size is calculated to ensure a power of 90% to detect statistical significance for the comparison of LCZ696-based treatment regimen with the olmesartan-based treatment regimen in assessing the superiority at the Week 12 endpoint, under the alternative hypothesis that the treatment difference is 6.5 mmHg at a two-sided significance level of 0.05. Assuming a 15% dropout rate, the total targeted sample size to be randomised is 432 patients (216 per group). The primary variable at the Week 12 endpoint will be analysed using a two-way analysis of covariance (ANCOVA), with treatment and region as factors and the baseline as a covariate. Mean CAPP at the Week 12 endpoint will be analysed using the same type of ANCOVA model used for the primary efficacy analysis.

DISCUSSION

Hypertension in patients over 60 years is often difficult to control because of age-associated adverse changes in vascular structure and function, especially arterial stiffening and the resulting changes in aortic haemodynamics. The majority of elderly patients present with features of arterial stiffening, notably ISH, disrupted circadian BP variation, a non-dipping or early morning riser phenotype of hypertension, and orthostatic hypertension. Moreover, compared with younger people, elderly patients are usually characterised with augmented aortic systolic and pulse pressures relative to brachial pressure, associated with diminished aortic-brachial pressure amplification resulting in the 'true' elevation of brachial systolic and pulse pressures. In turn, the elevated aortic and brachial pulse pressures that result from increased cardiac work to overcome the increased characteristic impedance of the aorta due to its age-related stiffening, causes an increased predisposition to left ventricular hypertrophy, myocardial ischaemia and heart failure.

Our hypothesis is that the ARNI LCZ696 provides a novel approach to neurohormonal modulation by concomitantly enhancing the NP system and suppressing the RAAS. Owing to the effects of enhanced NPs and RAAS inhibition, LCZ696 is anticipated to improve aortic stiffness, reduce characteristic impedance, and improve central haemodynamics. NPs inhibit the production and action of vasoconstrictor peptides, inhibit sympathetic outflow, and protect against excess salt and water retention.[41] NPs also inhibit cardiac growth or the development of compensatory cardiac hypertrophy and regulate CV function.[41] Inhibition of sympathetic tone might be beneficial in controlling morning surge in BP in elderly patients with hypertension.[42,43] Additionally, suppressing the RAAS offers the potential for many similar actions on CV structure and function as well as favourable effects on microcirculatory haemodynamics as evidenced by observations of reduced albuminuria and renal protection beyond what might have been anticipated from BP reduction alone.

It has already been demonstrated that LCZ696 provides superior reductions in msSBP and msDBP versus valsartan in an 8-week study including 1328 patients with mild-to-moderate hypertension. In addition, LCZ696 significantly reduced maSBP versus valsartan (between-treatment difference: LCZ696 200 mg versus valsartan 160 mg, −3.23 mm Hg, 95% CI −5.70 to −0.75; LCZ696 400 mg versus valsartan 320 mg,−5.14 mm Hg, 95% CI −7.70 to −2.59).

However, there was no significant treatment difference in maDBP reductions, thereby providing evidence of improvements in PP with LCZ696 versus valsartan. These findings are consistent with improvements in large artery function. Furthermore, BP control rates were significantly higher with LCZ696 200 mg than with 160 mg valsartan (46% [78/168] versus 33% [54/163], p = 0·0147). Importantly, in these studies, unlike the vasopeptidase inhibitor omapatrilat, LCZ696 was generally well tolerated without an incidence of angio-oedema during 8 weeks of treatment.[21]

The reported improvements in PP suggest the potential for LCZ696 to protect more effectively than the existing BP-lowering agents from several consequences of ISH and vascular stiffness, such as stroke and diastolic heart failure. However, in the study by Ruilope et al[21] CAP, central haemodynamics and arterial stiffness were not assessed, precluding a meticulous assessment of the mechanisms underpinning the superior antihypertensive properties of LCZ696.

In the PARAMETER study, the measurement of CAP should more accurately assess the loading conditions on the LV, myocardium, coronary arteries, cerebral vasculature, and therefore theoretically CAP should provide a basis for more effective protection against CV target organ damage and events compared with brachial pressures. In this regard, even in normotensive individuals, measurement of aortic BP enhances the ability to predict the target organ changes.[44]

The PARAMETER study was initiated in December 2012 with a novel design to evaluate central haemodynamics in elderly patients with ISH and a widened PP at 12 and 52 weeks of treatment with LCZ696 or ARB olmesartan. If the changes in CASP at 12 weeks (acute haemodynamic effect) are larger than that in SBP, this would support the hypothesis that LCZ696 has the potential to favourably impact aortic haemodynamics and improve ventricular-vascular coupling in elderly patients with aged aortas and ISH. Treatment differences in PWV at 52 weeks would further support a direct beneficial effect of LCZ696 on aortic stiffness due to structural changes, independent of MAP, as both treatment groups will be titrated to achieve similar BP control. The overall effect of LCZ696 on maBP (maSBP, maDBP and maPP), 24-hour BP variability (standard deviation, covariance), and circadian BP rhythms (nocturnal dipping status and morning surge) will also be assessed in

comparison with olmesartan. The study targets randomisation of 432 patients and final results are expected in 2015. The results of the PARAMETER study will impact the design of phase III studies assessing the CV protection potential of LCZ696 in elderly patients with ISH.

In addition to the PARAMETER study, the efficacy and safety of LCZ696 is being evaluated in related studies, for example, in comparison with olmesartan in elderly patients with mild-to-moderate hypertension, in patients with systolic hypertension and in patients with systolic hypertension who did not respond to olmesartan. Although it is hypothesised in the PARAMETER study that LCZ696 will be more effective at lowering both central aortic and brachial BP compared with olmesartan, it is also recognised that other agents may need to be added to reach recommended BP goals in the elderly patients with systolic hypertension. Both calcium channel blockers (CCBs, usually amlodipine) and diuretics are the most commonly used antihypertensive agents in combination with RAAS blockade for patients failing to achieve their BP goal with RAAS blockade monotherapy. Besides being very effective, such combination therapies of specific antihypertensive classes may also improve safety and tolerability. For example, addition of ARBs to CCBs has been shown to reduce the peripheral oedema associated with amlodipine monotherapy.[45] Similarly, diuretic-induced hypokalaemia has been shown to be attenuated when RAAS blockade is combined with diuretic therapy.[46] To further evaluate such combination therapies with LCZ696, the BP-lowering efficacy, safety and tolerability is being evaluated in combination with amlodipine in patients with mild-to-moderate hypertension who were non-responsive to amlodipine and in patients with systolic hypertension. There are also other trials investigating the efficacy and safety of LCZ696 in patients with severe hypertension and in patients with renal impairment.

In summary, the PARAMETER study will evaluate mechanisms associated with BP-lowering in elderly patients with an aged CV system as evidenced by systolic hypertension and a widened PP. The study will define whether LCZ696, a first-in-class ARNI is more effective in lowering CASP and CAPP than the ARB olmesartan and also explore whether this effect is related to a BP-independent reduction in arterial stiffening suggesting a novel

mechanism to target systolic hypertension, a major and increasingly important unmet therapeutic need in the management of hypertension in elderly patients.

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CONFLICTS OF INTERESTS

BW, JC, and KK have received honoraria from Novartis for consulting and presentations at scientific symposia. DZ, PC, AH, PB, and JZ are employees of Novartis and are thus eligible for Novartis stock and stock options.

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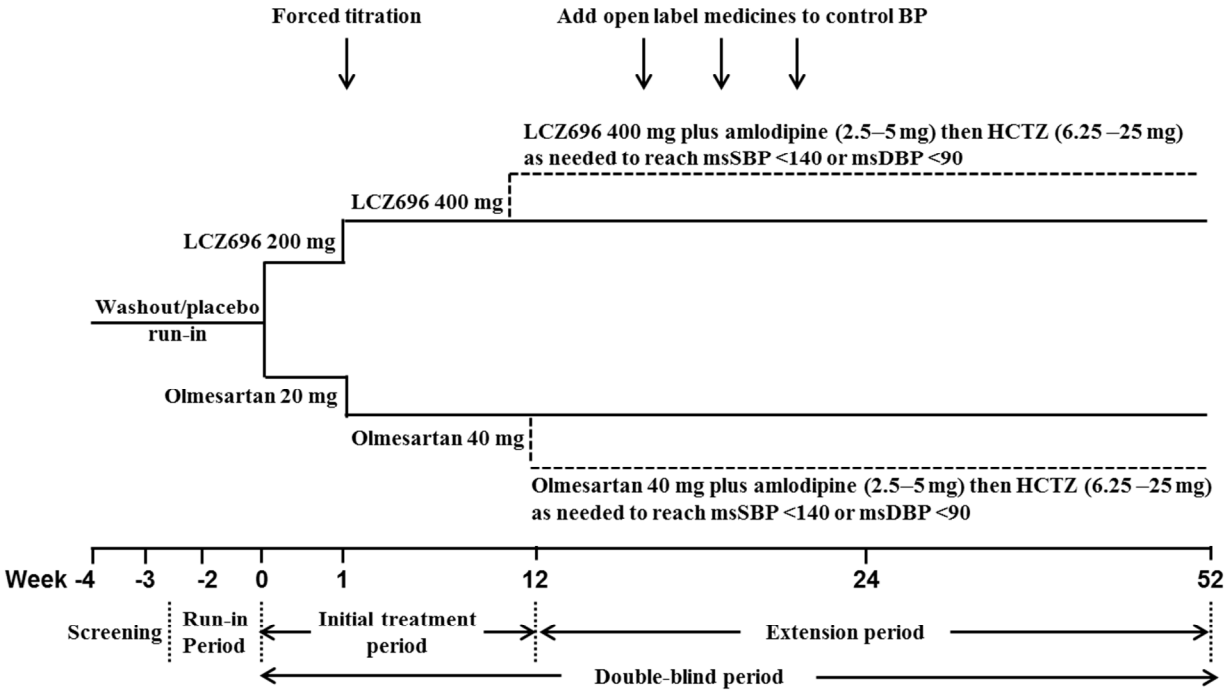
Figure 1. Study design



HCTZ, hydrochlorothiazide; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure

Box 1.

Inclusion criteria

- Patients with essential hypertension aged ≥60 years
- Either untreated or treated with antihypertensive agents, and who have msSBP ≥150 and <180 mm Hg at randomisation are eligible to be included.
    - Untreated patients (if they are newly diagnosed or have not been treated with antihypertensive drugs for the 4 weeks prior to screening) must have msSBP ≥150 mm Hg and <180 mm Hg at screening and randomisation.
    - Patients who have been treated with antihypertensive drugs during 4 weeks prior to screening must have msSBP ≥140 mm Hg and <180 mm Hg after 1 or 2 weeks of washout/placebo run-in and ≥150 mm Hg and <180 mm Hg at randomisation.
    - Patients must have a difference in msSBP of within ±15 mm Hg between randomisation and the visit preceding randomisation.
- All patients must have a PP>60 mmHg at randomisation.
- Patients who comply with all study requirements and demonstrate good medication compliance (≥80% compliance rate) during the amlodipine run-in period

Box 2.

Exclusion criteria

- Malignant or severe hypertension or secondary causes of hypertension
- History of atrial fibrillation or atrial flutter during 3 months prior to screening or active atrial fibrillation or atrial flutter on electrocardiogram during 12 months prior to screening
- History of cardiovascular disease (e.g., myocardial infarction) during the 12 months prior to screening
- Existing angina pectoris requiring pharmacological therapy (other than patients on a stable dose of oral or topical nitrates)
- Type 1 or type 2 diabetes mellitus not well controlled based on the investigator's clinical judgment
- Previous or current diagnosis of heart failure (NYHA Class II-IV), cardiac abnormalities such as Second or third degree atrioventricular block without a pacemaker, or malignancy
- Evidence of severe renal impairment (e.g., estimated glomerular filtration rate [eGFR] <30 ml/min//1.73 m^2
- Laboratory abnormalities such as serum potassium >5.5 mmol/L
- Known active liver disease or cirrhosis or evidence of hepatic disease
- Patients requiring any drug treatment that could affect BP
- Women of child bearing potential unless using highly effective methods of contraception during dosing

Rationale and study design of the Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker MEasuring arterial sTiffness in the eldERly (PARAMETER) study

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Rationale and study design of the Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker MEasuring arterial sTiffness in the eldERly (PARAMETER) study

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ABSTRACT Introduction; Methods and Analysis; Ethics and Dissemination.

Introduction: Hypertension in elderly people is characterised by elevated systolic blood pressure (SBP) and increased pulse pressure (PP), which indicate large artery ageing and stiffness. LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), is being developed to treat hypertension and heart failure. The Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker MEasuring arterial sTiffness in the eldERly (PARAMETER) study will assess the efficacy of LCZ696 versus olmesartan on aortic stiffness and central aortic haemodynamics.

Methods and Analysis: In this 52-week multicentre study, patients with hypertension aged ≥60 years with a mean seated (ms) SBP ≥150–<180mmHg and a PP>60mmHg will be randomised to once-daily LCZ696 200mg or olmesartan 20mg for 4 weeks, followed by a forced-titration to double the initial doses for the next 8 weeks. At 12–24 weeks, if the BP target has not been attained (msSBP <140mmHg and ms diastolic blood pressure <90 mmHg), amlodipine (2.5–5mg) and subsequently hydrochlorothiazide (6.25–25mg) can be added. The primary and secondary endpoints are changes from baseline in central aortic systolic pressure (CASP) and central aortic PP (CAPP) at Week 12, respectively. Other secondary endpoints are the changes in CASP and CAPP at Week 52. A sample size of 432 randomised patients is estimated to ensure a power of 90% to assess the superiority of LCZ696 over the olmesartan at Week 12 in the change from baseline of mean CASP, assuming a standard deviation of 19mmHg, the difference of 6.5mmHg and a 15% dropout rate. The primary variable will be analysed using a two-way analysis of covariance.

Ethics and Dissemination: The study was initiated in December 2012 and final results are expected in 2015. The results of this study will impact the design of future phase III studies assessing cardiovascular protection.

Clinical trials identifier: EUDract number 2012-002899-14 and ClinicalTrials.gov NCT01692301.

Key words: arterial stiffness, central aortic systolic pressure, isolated systolic hypertension, pulse pressure, LCZ696, elderly

Strengths and Weaknesses of this Study

Strengths:

- This is a randomized controlled trial of a new class of drug therapy (angiotensin receptor neprilysin inhibitor – ARNI) for hypertension versus a comparator that blocks only the angiotensin receptor – this will inform on the added value of neprilysin inhibition in the context of systolic hypertension;
- The study incorporates a detailed clinical experimental medicine mechanistic study that will interrogate the actions of this new drug class on vascular haemodynamics and function;
- The study evaluates the a novel treatment approach for a major unmet clinical need, i.e. systolic hypertension

Weaknesses

- The study has inadequate statistical power to assess the impact of the interventions on major clinical outcomes beyond blood pressure and vascular haemodynamics and function.

INTRODUCTION

Hypertension accounts for 9.4 million cardiovascular (CV) deaths annually worldwide and is affecting more than two-thirds of people aged ≥65 years, an age group that is growing globally.[1,2] The treatment of hypertension has been shown to reduce the risk of morbidity and mortality associated with elevated blood pressure (BP) including stroke, ischaemic heart disease, heart failure, chronic kidney disease and possibly cognitive decline.[3] Despite the availability of multiple drug classes with different mechanisms of action, hypertension, especially systolic blood pressure (SBP), remains inadequately controlled.[4,5,6]

The SBP usually increases from childhood throughout the life, while diastolic BP (DBP) remains relatively constant or decreases beyond 50 to 60 years of age. The changing patterns of BP throughout the life reflect different pathologies. In the young, hypertension is predominantly due to an increased DBP and mean arterial pressure (MAP), as a result of a relative increase in cardiac output and/or increased peripheral vascular resistance.[7] On the other hand, advancing age, beyond mid-life, is associated with an increased stiffness of large elastic arteries, especially the aorta. Arterial stiffening adversely affects the characteristic impedance of the aorta, requiring more cardiac work and raising SBP as more stroke volume is delivered during systole owing to the increased pulse wave velocity (PWV). DBP also decreases due to less elastic recoil leading to reduced flow, thus increasing PP independent of any changes in MAP. PWV been shown to be an independent predictor of CV outcomes, including mortality,[8] myocardial infarction (MI),[8] stroke,[8] atrial fibrillation,[9] cognitive decline[10] and renal dysfunction[11] and more specifically aortic PWV (aPWV), a robust measure of aortic arterial stiffness, has been shown to predict the adverse CV outcomes.[7]

Another consequence of arterial ageing and stiffening is that the amplification of SBP and PP from the aortic root to the peripheral arteries diminishes. In a healthy arterial system, central aortic systolic pressure (CASP) and PP are amplified as they move towards the periphery, such that the measured brachial systolic pressure is typically around 10 mm Hg higher than the corresponding aortic root pressure[12]. With ageing, this amplification is reduced because of the increased PWV and the increase in the early wave reflection resulting in the measured brachial SBP and PP becoming closer to the corresponding aortic root pressures. Some studies have suggested that central pressures may have a closer correlation than peripheral

BP with end organ damage[13-15] and CV risk,[15] such as extent of coronary atherosclerosis, carotid intima-media thickness, left ventricular hypertrophy, and left ventricular diastolic function.[14,16,17]

These observations raise the intriguing question as to whether treatments used to lower blood pressure could differentially affect aortic relative to brachial pressures and also arterial stiffness per se. It has been demonstrated that BP-lowering drugs can have marked differential effects on central aortic pressure (CAP) and brachial BP.[18] These effects mimic a functional anti-ageing effect in terms of their impact on wave-form morphology, and greater reduction in central pressures relative to brachial pressures. Intriguingly, the beta-blockers, a drug class which was least effective at lowering aortic pressure also appeared to be the least effective class at reducing the risk of stroke in elderly patients.[18] This supports the concept that the more effective lowering of aortic relative to brachial pressure may be clinically important.

Despite the findings cited above, controlling SBP remains the most important unmet need in the clinical management of hypertension. The rise in SBP and PP with ageing appears to be strongly related to arterial stiffening and increased impedance to flow through a stiff aorta. This suggests that the treatments targeting aortic stiffening and reducing characteristic impedance would be effective particularly at reducing systolic pressure. Early proof of this concept came from the studies with omapatrilat, a vasopeptidase inhibitor that simultaneously inhibits neprilysin and angiotensin-converting enzyme (ACE). Neprilysin inhibition enhances natriuretic peptide (NP) levels by blocking their degradation. NP has vasodilating actions, which could reduce aortic stiffness, improve characteristic impedance and thereby reduce SBP and PP. Studies with omapatrilat show greater improvements in aortic characteristic impedance compared with enalapril, beyond the effects of BP-lowering after 12 weeks of therapy.[19] This benefit on aortic function was also associated with impressive data on SBP and PP lowering in patients with hypertension.

Although omapatrilat was withdrawn due to safety concerns, a proof of concept was established for concomitant inhibition of neprilysin and renin-angiotensin-aldosterone system (RAAS) with the potential to be an attractive treatment strategy to improve aortic haemodynamics. Increased NP levels also promote natriuresis and reduce sympathetic tone,

together with antiproliferative and antihypertrophic effects, and inhibition of aldosterone secretion.[20] Alongside, suppression of RAAS would be complementary to neprilysin inhibition, which attenuates vasoconstriction, reduces sodium and water retention and also inhibits the development of CV hypertrophy and adverse re-modelling.

Recently LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), has been developed. LCZ696 delivers systemic exposure to a neprilysin inhibitor prodrug, AHU377 (which rapidly converts into active LBQ657), and an angiotensin receptor blocker (ARB), valsartan. LCZ696 at 100, 200 and 400 mg once daily, in patients with mild-to-moderate essential hypertension, resulted in greater BP reductions than corresponding doses of valsartan alone (160 and 320 mg) and was well tolerated.[21] LCZ696 compared with valsartan was effective especially at reducing brachial SBP and PP. Furthermore, in patients with heart failure with preserved ejection fraction, LCZ696 has shown to reduce N-terminal-pro B-type natriuretic peptide (NT-proBNP), a biomarker of left ventricular (LV) wall stress, to a greater extent than valsartan alone at 12 weeks and was well tolerated.[22]

Thus, the big challenge in hypertension treatment is to reduce the SBP, and the available evidence suggests that this could be achieved by improving the haemodynamic performance of the ageing aorta. The Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker MEasuring arterial sTiffness in the eldERly (PARAMETER) study is designed to compare the effect of LCZ696 with olmesartan, an ARB, on CASP, other measures of central aortic haemodynamics and arterial stiffness, and ambulatory blood pressures in elderly patients with an elevated brachial SBP and a widened PP. The widened PP was chosen as an entry criteria as being indicative of aortic stiffening and advanced aortic ageing. The objective is to determine whether the ARNI LCZ696 can reverse some of the effects of arterial ageing in elderly patients with systolic hypertension, and thereby improve aortic pressures and haemodynamics. The study was initiated in December 2012 and the final results are expected in 2015. This manuscript describes the design, objectives and pre-specified analysis plan for the PARAMETER study.

METHODS

Study design

The PARAMETER study is a 52-week, multicentre, randomised, double-blind, active-controlled, parallel-group study, involving 51 centres from 13 countries (Europe 47%, South America 14%, Asia 19% and US 20% — see online supplement for list of local investigators and participating centres). The study includes a screening period, a placebo run-in, and an initial double-blind treatment period of 12 weeks with LCZ696 monotherapy, followed by a double-blind extension of 40 weeks, during which add-on therapy is allowed to reach the BP treatment goal. Patients will be randomised to receive either once-daily LCZ696 200 mg or olmesartan 20 mg for 4 weeks, followed by a forced-titration to double the initial doses for the next 8 weeks. After 12 weeks, patients with uncontrolled BP (mean sitting [ms] SBP >140 mm Hg and/or msDBP >90 mm Hg) will be prescribed amlodipine (2.5–5 mg) and then hydrochlorothiazide (6.25–25 mg) as needed, at an interval of 4 weeks up to Week 24 (Figure 1). This study has been approved by all relevant ethics committees. The study is registered as EUDract number 2012-002899-14 and on ClinicalTrials.gov under the code NCT01692301.

Study participants

Elderly patients (aged ≥60 years) with essential hypertension (either untreated or treated with antihypertensive agents) and patients who have msSBP ≥150 mm Hg and <180 mm Hg at randomisation are eligible for inclusion in the study. Untreated patients (if they are newly diagnosed or have not been treated with antihypertensive drugs for the 4 weeks prior to screening) must have msSBP ≥150 mm Hg and <180 mm Hg at screening and randomisation, whereas patients who have been treated with antihypertensive agents 4 weeks prior to screening must have msSBP ≥140 mm Hg and <180 mm Hg after 1 or 2 weeks of washout/placebo run-in and ≥150 mm Hg and <180 mm Hg at randomisation. All patients must have a PP>60 mm Hg at randomisation. Patients with malignant or severe hypertension, secondary causes of hypertension, history of atrial fibrillation or atrial flutter during the 3 months prior to screening, or active atrial fibrillation or atrial flutter on electrocardiogram, history of CV disease (e.g., myocardial infarction) during 12 months prior to screening, and

evidence of severe renal impairment (e.g., estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) are excluded – boxes 1 and 2 summarise the inclusion and exclusion criteria, respectively. Patients have to provide a written informed consent before starting any study-related procedures.

The study objectives and endpoints

The primary objective of the study is to demonstrate the superiority of a LCZ696-based treatment regimen over an olmesartan-based treatment regimen in reducing mean CASP after 12 weeks of treatment. Superiority testing is also planned for the key secondary efficacy assessment, i.e. the reduction in mean central aortic PP (CAPP) after 12 weeks of treatment, and other secondary efficacy assessments such as mean CASP and CAPP after 52 weeks of treatment. Mean aPWV, msSBP, msDBP, msPP, mean ambulatory (ma) BP, maPP, and MAP will also be measured after 12 and 52 weeks of treatment.

Exploratory assessments comparing the two treatments after 12 and 52 weeks of treatment include pulse wave analysis (PWA) variables such as augmentation index (AIx), augmentation pressure, PP amplification ratio, duration of left ventricle (LV) ejection, and time to wave reflection; reduction in ma central (mac) BP, macMAP, and macPP; plasma biomarkers including NT-proBNP and urinary cyclic guanosine monophosphate (cGMP)/creatinine ratio and other biomarkers related to hypertension.

Haemodynamic measurements

The SphygmoCor X-CEL System (AtCor Medical, Sydney, Australia) is being used to non-invasively derive the ascending aortic pressure waveform from the brachial waveform using a validated generalised transfer function (GTF).[23] A properly sized BP cuff is linked to a computer and software and the CASP, CAPP, augmentation pressure, and AIx are determined from the analysis of waveform by the system software.

The SphygmoCor X-CEL system also measures the carotid-femoral aPWV, as the speed of the arterial pressure waveform as it travels through the descending aorta to the femoral artery, which is detected from simultaneously measured carotid and femoral arterial pulses. The carotid pulse is detected by applanation tonometry using a high-fidelity pressure

transducer (Millar Instruments, Houston, TX), while the femoral pulse is detected using a partially inflated blood pressure cuff wrapped around the upper thigh. The distance travelled by the pulse wave is captured by making physical measurements on the body surface according to the manufacturer's recommendations. This new brachial cuff-based device with an individualised sub-diastolic cuff pressure has recently been validated against the SphygmoCor device (AtCor Medical) using the classical radial tonometry-based methodology, and provides an operator-independent method to assess systolic pressure and aortic waveform comparable with the existing validated tonometric-based methods.[24] Measurements using SphygmoCor X-CEL system will be performed at baseline, randomisation, Week 12 or at the time of early discontinuation prior to Week 12, Week 52, or at the time of early discontinuation between Week 12 and Week 52.

The 24-hour maCAP and maPWA will be monitored using the oscillometric device, Mobil-O-Graph (IEM, Stolberg, Germany) with integrated ARC solver algorithms (Austrian Institute of Technology, Vienna, Austria). The traditional Mobil-O-Graph ambulatory blood pressure monitoring (ABPM) device has been available for more than a decade and through several product generations.[25-28] The actual blood pressure measuring unit was validated according to the British Hypertension Society (BHS) and the European Society of Hypertension (ESH) recommendations.[25,27] The method equipped with a GTF to derive aortic pressure waveforms[29] is based on brachial readings acquired in the course of the conventional pressure measurement at diastolic level.

During the signal acquisition procedure, the received raw signals are separated into single waves and checked for their plausibility by means of extreme values and corresponding wavelengths using a cross-correlation approach. Poor waveforms are removed from further processing. After applying the GTF to each single waveform, the procedure is repeated. After final coherence verification, the quality judgment of grade '1' states that at least 80% of the waveforms were found to be eligible for further processing, while grades '2' and '3' represent a ≥50% and <50% valid waveforms, respectively.[30]

Surrogates derived by this technique have been validated against solid-state catheter measurements and/or compared with non-invasive readings (e.g., tonometry, echocardiography) for aortic pressures,[30-33] wave reflections,[34] or aPWV.[35,36] However,

potential clinical usefulness has been demonstrated recently.[37-39] Furthermore, feasibility[36] and reproducibility[40] of cuff-based maPWA measurements have been reported. With respect to legal issues, the Mobil-O-Graph maPWA monitor with integrated ARC solver algorithms holds approvals from CE, FDA, and JPAL (amongst others).

Safety assessments

Safety and tolerability assessments include regular monitoring and recording of all adverse events (AEs) and concomitant medications or significant non-drug therapies. Evaluations of routine blood chemistries, blood counts with white cell differential and urine analyses, physical examinations, electrocardiograms (ECGs), and monitoring of vital signs will be performed at regular intervals.

Statistical analysis plan

A sample size of 183 completers per group is targeted, which is calculated based on the primary efficacy variable, change from baseline in mean CASP at 12 weeks, assuming a standard deviation of 19 mm Hg. The sample size is calculated to ensure a power of 90% to detect statistical significance for the comparison of LCZ696-based treatment regimen with the olmesartan-based treatment regimen in assessing the superiority at the Week 12 endpoint, under the alternative hypothesis that the treatment difference is 6.5 mmHg at a two-sided significance level of 0.05. Assuming a 15% dropout rate, the total targeted sample size to be randomised is 432 patients (216 per group). The primary variable at the Week 12 endpoint will be analysed using a two-way analysis of covariance (ANCOVA), with treatment and region as factors and the baseline as a covariate. Mean CAPP at the Week 12 endpoint will be analysed using the same type of ANCOVA model used for the primary efficacy analysis.

DISCUSSION

Hypertension in patients over 60 years is often difficult to control because of age-associated adverse changes in vascular structure and function, especially arterial stiffening and the resulting changes in aortic haemodynamics. The majority of elderly patients present with features of arterial stiffening, notably ISH, disrupted circadian BP variation, a non-dipping or early morning riser phenotype of hypertension, and orthostatic hypertension. Moreover, compared with younger people, elderly patients are usually characterised with augmented aortic systolic and pulse pressures relative to brachial pressure, associated with diminished aortic-brachial pressure amplification resulting in the 'true' elevation of brachial systolic and pulse pressures. In turn, the elevated aortic and brachial pulse pressures that result from increased cardiac work to overcome the increased characteristic impedance of the aorta due to its age-related stiffening, causes an increased predisposition to left ventricular hypertrophy, myocardial ischaemia and heart failure.

Our hypothesis is that the ARNI LCZ696 provides a novel approach to neurohormonal modulation by concomitantly enhancing the NP system and suppressing the RAAS. Owing to the effects of enhanced NPs and RAAS inhibition, LCZ696 is anticipated to improve aortic stiffness, reduce characteristic impedance, and improve central haemodynamics. NPs inhibit the production and action of vasoconstrictor peptides, inhibit sympathetic outflow, and protect against excess salt and water retention.[41] NPs also inhibit cardiac growth or the development of compensatory cardiac hypertrophy and regulate CV function.[41] Inhibition of sympathetic tone might be beneficial in controlling morning surge in BP in elderly patients with hypertension.[42,43] Additionally, suppressing the RAAS offers the potential for many similar actions on CV structure and function as well as favourable effects on microcirculatory haemodynamics as evidenced by observations of reduced albuminuria and renal protection beyond what might have been anticipated from BP reduction alone.

It has already been demonstrated that LCZ696 provides superior reductions in msSBP and msDBP versus valsartan in an 8-week study including 1328 patients with mild-to-moderate hypertension. In addition, LCZ696 significantly reduced maSBP versus valsartan (between-treatment difference: LCZ696 200 mg versus valsartan 160 mg, −3.23 mm Hg, 95% CI −5.70 to −0.75; LCZ696 400 mg versus valsartan 320 mg,−5.14 mm Hg, 95% CI −7.70 to −2.59).

However, there was no significant treatment difference in maDBP reductions, thereby providing evidence of improvements in PP with LCZ696 versus valsartan. These findings are consistent with improvements in large artery function. Furthermore, BP control rates were significantly higher with LCZ696 200 mg than with 160 mg valsartan (46% [78/168] versus 33% [54/163], p = 0·0147). Importantly, in these studies, unlike the vasopeptidase inhibitor omapatrilat, LCZ696 was generally well tolerated without an incidence of angio-oedema during 8 weeks of treatment.[21]

The reported improvements in PP suggest the potential for LCZ696 to protect more effectively than the existing BP-lowering agents from several consequences of ISH and vascular stiffness, such as stroke and diastolic heart failure. However, in the study by Ruilope et al[21] CAP, central haemodynamics and arterial stiffness were not assessed, precluding a meticulous assessment of the mechanisms underpinning the superior antihypertensive properties of LCZ696.

In the PARAMETER study, the measurement of CAP should more accurately assess the loading conditions on the LV, myocardium, coronary arteries, cerebral vasculature, and therefore theoretically CAP should provide a basis for more effective protection against CV target organ damage and events compared with brachial pressures. In this regard, even in normotensive individuals, measurement of aortic BP enhances the ability to predict the target organ changes.[44]

The PARAMETER study was initiated in December 2012 with a novel design to evaluate central haemodynamics in elderly patients with ISH and a widened PP at 12 and 52 weeks of treatment with LCZ696 or ARB olmesartan. If the changes in CASP at 12 weeks (acute haemodynamic effect) are larger than that in SBP, this would support the hypothesis that LCZ696 has the potential to favourably impact aortic haemodynamics and improve ventricular-vascular coupling in elderly patients with aged aortas and ISH. Treatment differences in PWV at 52 weeks would further support a direct beneficial effect of LCZ696 on aortic stiffness due to structural changes, independent of MAP, as both treatment groups will be titrated to achieve similar BP control. The overall effect of LCZ696 on maBP (maSBP, maDBP and maPP), 24-hour BP variability (standard deviation, covariance), and circadian BP rhythms (nocturnal dipping status and morning surge) will also be assessed in

comparison with olmesartan. The study targets randomisation of 432 patients and final results are expected in 2015. We acknowledge the limitations of this study which is designed to look at surrogate markers rather than major cardiovascular outcomes, nevertheless, this is important to establish if there are differential effects of drugs therapies on surrogate outcomes of cardiovascular disease to justify and impact on the design of subsequent phase III studies assessing the potential of LCZ696 for enhanced cardiovascular disease and stroke prevention in elderly patients with ISH.

In addition to the PARAMETER study, the efficacy and safety of LCZ696 is being evaluated in related studies, for example, in comparison with olmesartan in elderly patients with mild-to-moderate hypertension, in patients with systolic hypertension and in patients with systolic hypertension who did not respond to olmesartan. Although it is hypothesised in the PARAMETER study that LCZ696 will be more effective at lowering both central aortic and brachial BP compared with olmesartan, it is also recognised that other agents may need to be added to reach recommended BP goals in the elderly patients with systolic hypertension. Both calcium channel blockers (CCBs, usually amlodipine) and diuretics are the most commonly used antihypertensive agents in combination with RAAS blockade for patients failing to achieve their BP goal with RAAS blockade monotherapy. Besides being very effective, such combination therapies of specific antihypertensive classes may also improve safety and tolerability. For example, addition of ARBs to CCBs has been shown to reduce the peripheral oedema associated with amlodipine monotherapy.[45] Similarly, diuretic-induced hypokalaemia has been shown to be attenuated when RAAS blockade is combined with diuretic therapy.[46] To further evaluate such combination therapies with LCZ696, the BP-lowering efficacy, safety and tolerability is being evaluated in combination with amlodipine in patients with mild-to-moderate hypertension who were non-responsive to amlodipine and in patients with systolic hypertension. There are also other trials investigating the efficacy and safety of LCZ696 in patients with severe hypertension and in patients with renal impairment.

In summary, the PARAMETER study will evaluate mechanisms associated with BP-lowering in elderly patients with an aged CV system as evidenced by systolic hypertension and a widened PP. The study will define whether LCZ696, a first-in-class ARNI is more

effective in lowering CASP and CAPP than the ARB olmesartan and also explore whether this effect is related to a BP-independent reduction in arterial stiffening, suggesting a novel mechanism to target systolic hypertension, a major and increasingly important unmet therapeutic need in the management of hypertension in elderly patients.

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CONFLICTS OF INTERESTS

BW, JC, and KK have received honoraria from Novartis for consulting and presentations at scientific symposia. DZ, PC, AH, PB, and JZ are employees of Novartis and are thus eligible for Novartis stock and stock options.

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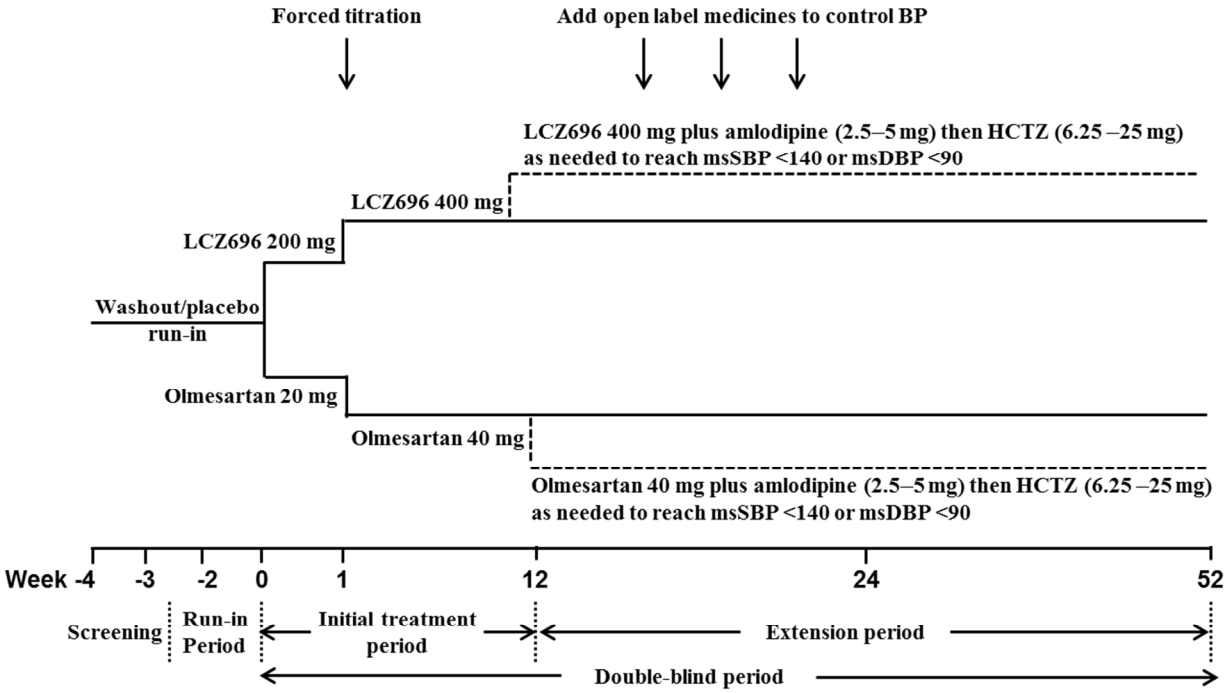
Figure 1. Study design



HCTZ, hydrochlorothiazide; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure

Box 1.

Inclusion criteria

- Patients with essential hypertension aged ≥60 years
- Either untreated or treated with antihypertensive agents, and who have msSBP ≥150 and <180 mm Hg at randomisation are eligible to be included.
    - Untreated patients (if they are newly diagnosed or have not been treated with antihypertensive drugs for the 4 weeks prior to screening) must have msSBP ≥150 mm Hg and <180 mm Hg at screening and randomisation.
    - Patients who have been treated with antihypertensive drugs during 4 weeks prior to screening must have msSBP ≥140 mm Hg and <180 mm Hg after 1 or 2 weeks of washout/placebo run-in and ≥150 mm Hg and <180 mm Hg at randomisation.
    - Patients must have a difference in msSBP of within ±15 mm Hg between randomisation and the visit preceding randomisation.
- All patients must have a PP>60 mmHg at randomisation.
- Patients who comply with all study requirements and demonstrate good medication compliance (≥80% compliance rate) during the amlodipine run-in period

Box 2.

Exclusion criteria

- Malignant or severe hypertension or secondary causes of hypertension
- History of atrial fibrillation or atrial flutter during 3 months prior to screening or active atrial fibrillation or atrial flutter on electrocardiogram during 12 months prior to screening
- History of cardiovascular disease (e.g., myocardial infarction) during the 12 months prior to screening
- Existing angina pectoris requiring pharmacological therapy (other than patients on a stable dose of oral or topical nitrates)
- Type 1 or type 2 diabetes mellitus not well controlled based on the investigator's clinical judgment
- Previous or current diagnosis of heart failure (NYHA Class II-IV), cardiac abnormalities such as Second or third degree atrioventricular block without a pacemaker, or malignancy
- Evidence of severe renal impairment (e.g., estimated glomerular filtration rate [eGFR] <30 ml/min//1.73 m^2
- Laboratory abnormalities such as serum potassium >5.5 mmol/L
- Known active liver disease or cirrhosis or evidence of hepatic disease
- Patients requiring any drug treatment that could affect BP
- Women of child bearing potential unless using highly effective methods of contraception during dosing

Rationale and study design of the Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker MEasuring arterial sTiffness in the eldERly (PARAMETER) study

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ABSTRACT

IntroductionBackground: Hypertension in elderly people is characterised by elevated systolic blood pressure (SBP) and increased pulse pressure (PP), which indicate large artery ageing and stiffness. LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), is currently being developed to treatfor the treatment of hypertension and heart failure. The Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker MEasuring arterial sTiffness in the eldERly (PARAMETER) study will assess the efficacy of LCZ696 versus olmesartan on aortic stiffness and central aortic haemodynamics.

MethodsDesign and Analysismethods: In this 52-week multicentre study, patients with hypertension aged ≥60 years with a mean seated (ms) SBP ≥150–<180mmHg and a PP>60mmHg will be randomised to once-daily LCZ696 200mg or olmesartan 20mg for 4 weeks, followed by a forced-titration to double the initial doses for the next 8 weeks. At 12–24 weeks, if the BP target has not been attained (msSBP <140mmHg and ms diastolic blood pressure <90 mmHg), amlodipine (2.5–5mg) and subsequently hydrochlorothiazide (6.25–25mg) can be added. The primary and secondary endpoints are changes from baseline in central aortic systolic pressure (CASP) and central aortic PP (CAPP) at Week 12, respectively. Other secondary endpoints are the changes in CASP and CAPP at Week 52.

Statistical analysis plan: A sample size of 432 randomised patients is estimated to ensure a power of 90% to assess the superiority of LCZ696 over the olmesartan at Week 12 in the change from baseline of mean CASP, assuming a standard deviation of 19mmHg, the difference of 6.5mmHg and a 15% dropout rate. The primary variable will be analysed using a two-way analysis of covariance.

Ethics and DisseminationProgress and implications: The study was initiated in December 2012 and final results are expected in 2015. The results of this study will impact the design of future phase III studies assessing cardiovascular protection.

Clinical trials identifier: EUDract number 2012-002899-14 and ClinicalTrials.gov NCT01692301.

Key words: arterial stiffness, central aortic systolic pressure, isolated systolic hypertension, pulse pressure, LCZ696, elderly

Strengths and Weaknesses of this Study

Strengths:

- This is a randomized controlled trial of a new class of drug therapy (angiotensin receptor neprilysin inhibitor – ARNI) for hypertension versus a comparator that blocks only the angiotensin receptor – this will inform on the added value of neprilysin inhibition in the context of systolic hypertension;
- The study incorporates a detailed clinical experimental medicine mechanistic study that will interrogate the actions of this new drug class on vascular haemodynamics and function;
- The study evaluates the a novel treatment approach for a major unmet clinical need, i.e. systolic hypertension

Weaknesses

- The study has inadequate statistical power to assess the impact of the interventions on major clinical outcomes beyond blood pressure and vascular haemodynamics and function.

INTRODUCTION

Hypertension accounts for 9.4 million cardiovascular (CV) deaths annually worldwide and is affecting more than two-thirds of people aged ≥65 years, an age group that is growing globally.[1,2] The treatment of hypertension has been shown to reduce the risk of morbidity and mortality associated with elevated blood pressure (BP) including stroke, ischaemic heart disease, heart failure, chronic kidney disease and possibly cognitive decline.[3] Despite the availability of multiple drug classes with different mechanisms of action, hypertension, especially systolic blood pressure (SBP), remains inadequately controlled.[4,5,6]

The SBP usually increases from childhood throughout the life, while diastolic BP (DBP) remains relatively constant or decreases beyond 50 to 60 years of age. ~~This indicates that the worldwide burden of hypertension beyond 50 to 60 years is mostly due to systolic hypertension. Furthermore, the progressive increase in SBP and decrease or no change in DBP widens pulse pressure (PP), and results in the development of isolated systolic hypertension (ISH), which is the predominant form of hypertension in elderly patients. The National Health and Nutrition Examination Survey (NHANES) III reported that the prevalence of ISH was 87% in elderly patients with hypertension.[5] Furthermore, the Framingham Heart Study (FHS) reported almost a 90% lifetime risk of developing ISH in normotensive people reaching the age of 65 years and who survived for another 20 to 25 years.[6]~~

The changing patterns of BP throughout the life reflect different pathologies. In the young, hypertension is predominantly due to an increased DBP and mean arterial pressure (MAP), as a result of a relative increase in cardiac output and/or increased peripheral vascular resistance.[7] On the other hand, advancing age, beyond mid-life, is associated with an increased stiffness of large elastic arteries, especially the aorta. Arterial stiffening adversely affects the characteristic impedance of the aorta, requiring more cardiac work and raising SBP as more stroke volume is delivered during systole owing to the increased pulse wave velocity (PWV). DBP also decreases due to less elastic recoil leading to reduced flow, thus increasing PP independent of any changes in MAP. PWV been shown to be an independent predictor of CV outcomes, including mortality,[8] myocardial infarction (MI),[8] stroke,[8] atrial fibrillation,[9] cognitive decline[10] and renal dysfunction[11] and more specifically aortic PWV

(aPWV), a robust measure of aortic arterial stiffness, has been shown to predict the adverse CV outcomes.[7]

Another consequence of arterial ageing and stiffening is that the amplification of SBP and PP from the aortic root to the peripheral arteries diminishes. In a healthy arterial system, central aortic systolic pressure (CASP) and PP are amplified as they move towards the periphery, such that the measured brachial systolic pressure is typically around 10–mm Hg higher than the corresponding aortic root pressure[12]. With ageing, this amplification is reduced because of the increased PWV and the increase in the early wave reflection resulting in the measured brachial SBP and PP becoming closer to the corresponding aortic root pressures. Some studies have suggested that central pressures may have a closer correlation than peripheral BP with end organ damage[13-15] and CV risk,[15] such as extent of coronary atherosclerosis, carotid intima-media thickness, left ventricular hypertrophy, and left ventricular diastolic function.[14,16,17]

These observations raise the intriguing question as to whether treatments used to lower blood pressure could differentially affect aortic relative to brachial pressures and also arterial stiffness per se. It has been demonstrated that BP-lowering drugs can have marked differential effects on central aortic pressure (CAP) and brachial BP.[18] These effects mimic a functional anti-ageing effect in terms of their impact on wave-form morphology, and greater reduction in central pressures relative to brachial pressures. Intriguingly, the beta-blockers, a drug class which was least effective at lowering aortic pressure also appeared to be the least effective class at reducing the risk of stroke in elderly patients.[18] This supports the concept that the more effective lowering of aortic relative to brachial pressure may be clinically important.

Despite the findings cited above, controlling SBP remains the most important unmet need in the clinical management of hypertension. The rise in SBP and PP with ageing appears to be strongly related to arterial stiffening and increased impedance to flow through a stiff aorta. This suggests that the treatments targeting aortic stiffening and reducing characteristic impedance would be effective particularly at reducing systolic pressure. Early proof of this concept came from the studies with omapatrilat, a vasopeptidase inhibitor that simultaneously inhibits neprilysin and angiotensin-converting enzyme (ACE). Neprilysin

inhibition enhances natriuretic peptide (NP) levels by blocking their degradation. NP has vasodilating actions, which could reduce aortic stiffness, improve characteristic impedance and thereby reduce SBP and PP. Studies with omapatrilat show greater improvements in aortic characteristic impedance compared with enalapril, beyond the effects of BP-lowering after 12 weeks of therapy.[19] This benefit on aortic function was also associated with impressive data on SBP and PP lowering in patients with hypertension. ~~Despite this considerable promise, omapatrilat was withdrawn due to safety concerns owing to increased incidences of angio-oedema associated with the ACE-inhibitor component, which was seemingly potentiated by the neprilysin inhibition.~~

Although omapatrilat was withdrawn due to safety concerns, ~~Nevertheless,~~ a proof of concept was established for concomitant inhibition of neprilysin and renin-angiotensin-aldosterone system (RAAS) with the potential to be an attractive treatment strategy to improve aortic haemodynamics. ~~Furthermore, there might be other benefits of neprilysin inhibition in the setting of hypertension, beyond its vasodilator action.~~ Increased NP levels also promote natriuresis and reduce sympathetic tone, together with antiproliferative and antihypertrophic effects, and inhibition of aldosterone secretion.[20] Alongside, suppression of RAAS would be complementary to neprilysin inhibition, which attenuates vasoconstriction, reduces sodium and water retention and also inhibits the development of CV hypertrophy and adverse re-modelling.

Recently LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), has been developed. LCZ696 delivers systemic exposure to a neprilysin inhibitor prodrug, AHU377 (which rapidly converts into active LBQ657), and an angiotensin receptor blocker (ARB), valsartan. LCZ696 at 100, 200 and 400 mg once daily, in patients with mild-to-moderate essential hypertension, resulted in greater BP reductions than corresponding doses of valsartan alone (160 and 320 mg) and was well tolerated.[21] LCZ696 compared with valsartan was effective especially at reducing brachial SBP and PP. Furthermore, in patients with heart failure with preserved ejection fraction, LCZ696 has shown to reduce N-terminal-pro B-type natriuretic peptide (NT-proBNP), a biomarker of left ventricular (LV) wall stress, to a greater extent than valsartan alone at 12 weeks and was well tolerated.[22]

Thus, the big challenge in hypertension treatment is to reduce the SBP, and the available evidence suggests that this could be achieved by improving the haemodynamic performance of the ageing aorta. The Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker MEasuring arterial sTiffness in the eldERly (PARAMETER) study is designed to compare the effect of LCZ696 with olmesartan, an ARB, on CASP, other measures of central aortic haemodynamics and arterial stiffness, and ambulatory blood pressures in elderly patients with an elevated brachial SBP and a widened PP. The widened PP was chosen as an entry criteria as being indicative of aortic stiffening and advanced aortic ageing. The objective is to determine whether the ARNI LCZ696 can reverse some of the effects of arterial ageing in elderly patients with systolic hypertension, and thereby improve aortic pressures and haemodynamics. The study was initiated in December 2012 and the final results are expected in 2015. This manuscript describes the design, objectives and pre-specified analysis plan for the PARAMETER study.

METHODS

Study design

The PARAMETER study is a 52-week, multicentre, randomised, double-blind, active-controlled, parallel-group study, involving 51 centres from 13 countries (Europe 47%, South America 14%, Asia 19% and US 20% — see online supplement for list of local investigators and participating centres). The study includes a screening period, a placebo run-in, and an initial double-blind treatment period of 12 weeks with LCZ696 monotherapy, followed by a double-blind extension of 40 weeks, during which add-on therapy is allowed to reach the BP treatment goal. Patients will be randomised to receive either once-daily LCZ696 200 mg or olmesartan 20 mg for 4 weeks, followed by a forced-titration to double the initial doses for the next 8 weeks. After 12 weeks, patients with uncontrolled BP (mean sitting [ms] SBP >140 mm Hg and/or msDBP >90 mm Hg) will be prescribed amlodipine (2.5–5 mg) and then hydrochlorothiazide (6.25–25 mg) as needed, at an interval of 4 weeks up to Week 24 (Figure 1). This study has been approved by all relevant ethics committees. The study is registered as EUDract number 2012-002899-14 and on ClinicalTrials.gov under the code NCT01692301.

Study participants

Elderly patients (aged ≥60 years) with essential hypertension (either untreated or treated with antihypertensive agents) and patients who have msSBP ≥150 mm Hg and <180 mm Hg at randomisation are eligible for inclusion in the study. Untreated patients (if they are newly diagnosed or have not been treated with antihypertensive drugs for the 4 weeks prior to screening) must have msSBP ≥150 mm Hg and <180 mm Hg at screening and randomisation, whereas patients who have been treated with antihypertensive agents 4 weeks prior to screening must have msSBP ≥140 mm Hg and <180 mm Hg after 1 or 2 weeks of washout/placebo run-in and ≥150 mm Hg and <180 mm Hg at randomisation. All patients must have a PP>60 mm Hg at randomisation. Patients with malignant or severe hypertension, secondary causes of hypertension, history of atrial fibrillation or atrial flutter during the 3 months prior to screening, or active atrial fibrillation or atrial flutter on electrocardiogram, history of CV disease (e.g., myocardial infarction) during 12 months prior to screening, and

evidence of severe renal impairment (e.g., estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) are excluded – boxes 1 and 2 summarise the inclusion and exclusion criteria, respectively. Patients have to provide a written informed consent before starting any study-related procedures.

The study objectives and endpoints

The primary objective of the study is to demonstrate the superiority of a LCZ696-based treatment regimen over an olmesartan-based treatment regimen in reducing mean CASP after 12 weeks of treatment. Superiority testing is also planned for the key secondary efficacy assessment, i.e. the reduction in mean central aortic PP (CAPP) after 12 weeks of treatment, and other secondary efficacy assessments such as mean CASP and CAPP after 52 weeks of treatment. Mean aPWV, msSBP, msDBP, msPP, mean ambulatory (ma) BP, maPP, and MAP will also be measured after 12 and 52 weeks of treatment.

Exploratory assessments comparing the two treatments after 12 and 52 weeks of treatment include pulse wave analysis (PWA) variables such as augmentation index (AIx), augmentation pressure, PP amplification ratio, duration of left ventricle (LV) ejection, and time to wave reflection; reduction in ma central (mac) BP, macMAP, and macPP; plasma biomarkers including NT-proBNP and urinary cyclic guanosine monophosphate (cGMP)/creatinine ratio and other biomarkers related to hypertension.

Haemodynamic measurements

The SphygmoCor X-CEL System (AtCor Medical, Sydney, Australia) is being used to non-invasively derive the ascending aortic pressure waveform from the brachial waveform using a validated generalised transfer function (GTF).[23] A properly sized BP cuff is linked to a computer and software and the CASP, CAPP, augmentation pressure, and AIx are determined from the analysis of waveform by the system software.

The SphygmoCor X-CEL system also measures the carotid-femoral aPWV, as the speed of the arterial pressure waveform as it travels through the descending aorta to the femoral artery, which is detected from simultaneously measured carotid and femoral arterial pulses. The carotid pulse is detected by applanation tonometry using a high-fidelity pressure

transducer (Millar Instruments, Houston, TX), while the femoral pulse is detected using a partially inflated blood pressure cuff wrapped around the upper thigh. The distance travelled by the pulse wave is captured by making physical measurements on the body surface according to the manufacturer's recommendations. This new brachial cuff-based device with an individualised sub-diastolic cuff pressure has recently been validated against the SphygmoCor device (AtCor Medical) using the classical radial tonometry-based methodology, and provides an operator-independent method to assess systolic pressure and aortic waveform comparable with the existing validated tonometric-based methods.[24] Measurements using SphygmoCor X-CEL system will be performed at baseline, randomisation, Week 12 or at the time of early discontinuation prior to Week 12, Week 52, or at the time of early discontinuation between Week 12 and Week 52.

The 24-hour maCAP and maPWA will be monitored using the oscillometric device, Mobil-O-Graph (IEM, Stolberg, Germany) with integrated ARC solver algorithms (Austrian Institute of Technology, Vienna, Austria). The traditional Mobil-O-Graph ambulatory blood pressure monitoring (ABPM) device has been available for more than a decade and through several product generations.[25-28] The actual blood pressure measuring unit was validated according to the British Hypertension Society (BHS) and the European Society of Hypertension (ESH) recommendations.[25,27] The method equipped with a GTF to derive aortic pressure waveforms[29] is based on brachial readings acquired in the course of the conventional pressure measurement at diastolic level.

During the signal acquisition procedure, the received raw signals are separated into single waves and checked for their plausibility by means of extreme values and corresponding wavelengths using a cross-correlation approach. Poor waveforms are removed from further processing. After applying the GTF to each single waveform, the procedure is repeated. After final coherence verification, the quality judgment of grade '1' states that at least 80% of the waveforms were found to be eligible for further processing, while grades '2' and '3' represent a ≥50% and <50% valid waveforms, respectively.[30]

Surrogates derived by this technique have been validated against solid-state catheter measurements and/or compared with non-invasive readings (e.g., tonometry, echocardiography) for aortic pressures,[30-33] wave reflections,[34] or aPWV.[35,36] However,

potential clinical usefulness has been demonstrated recently.[37-39] Furthermore, feasibility[36] and reproducibility[40] of cuff-based maPWA measurements have been reported. With respect to legal issues, the Mobil-O-Graph maPWA monitor with integrated ARC solver algorithms holds approvals from CE, FDA, and JPAL (amongst others).

Safety assessments

Safety and tolerability assessments include regular monitoring and recording of all adverse events (AEs) and concomitant medications or significant non-drug therapies. Evaluations of routine blood chemistries, blood counts with white cell differential and urine analyses, physical examinations, electrocardiograms (ECGs), and monitoring of vital signs will be performed at regular intervals.

Statistical analysis plan

A sample size of 183 completers per group is targeted, which is calculated based on the primary efficacy variable, change from baseline in mean CASP at 12 weeks, assuming a standard deviation of 19 mm Hg. The sample size is calculated to ensure a power of 90% to detect statistical significance for the comparison of LCZ696-based treatment regimen with the olmesartan-based treatment regimen in assessing the superiority at the Week 12 endpoint, under the alternative hypothesis that the treatment difference is 6.5 mmHg at a two-sided significance level of 0.05. Assuming a 15% dropout rate, the total targeted sample size to be randomised is 432 patients (216 per group). The primary variable at the Week 12 endpoint will be analysed using a two-way analysis of covariance (ANCOVA), with treatment and region as factors and the baseline as a covariate. Mean CAPP at the Week 12 endpoint will be analysed using the same type of ANCOVA model used for the primary efficacy analysis.

DISCUSSION

Hypertension in patients over 60 years is often difficult to control because of age-associated adverse changes in vascular structure and function, especially arterial stiffening and the resulting changes in aortic haemodynamics. The majority of elderly patients present with features of arterial stiffening, notably ISH, disrupted circadian BP variation, a non-dipping or early morning riser phenotype of hypertension, and orthostatic hypertension. Moreover, compared with younger people, elderly patients are usually characterised with augmented aortic systolic and pulse pressures relative to brachial pressure, associated with diminished aortic-brachial pressure amplification resulting in the 'true' elevation of brachial systolic and pulse pressures. In turn, the elevated aortic and brachial pulse pressures that result from increased cardiac work to overcome the increased characteristic impedance of the aorta due to its age-related stiffening, causes an increased predisposition to left ventricular hypertrophy, myocardial ischaemia and heart failure.

Our hypothesis is that the ARNI LCZ696 provides a novel approach to neurohormonal modulation by concomitantly enhancing the NP system and suppressing the RAAS. Owing to the effects of enhanced NPs and RAAS inhibition, LCZ696 is anticipated to improve aortic stiffness, reduce characteristic impedance, and improve central haemodynamics. NPs inhibit the production and action of vasoconstrictor peptides, inhibit sympathetic outflow, and protect against excess salt and water retention.[41] NPs also inhibit cardiac growth or the development of compensatory cardiac hypertrophy and regulate CV function.[41] Inhibition of sympathetic tone might be beneficial in controlling morning surge in BP in elderly patients with hypertension.[42,43] Additionally, suppressing the RAAS offers the potential for many similar actions on CV structure and function as well as favourable effects on microcirculatory haemodynamics as evidenced by observations of reduced albuminuria and renal protection beyond what might have been anticipated from BP reduction alone.

It has already been demonstrated that LCZ696 provides superior reductions in msSBP and msDBP versus valsartan in an 8-week study including 1328 patients with mild-to-moderate hypertension. In addition, LCZ696 significantly reduced maSBP versus valsartan (between-treatment difference: LCZ696 200 mg versus valsartan 160 mg, −3.23 mm Hg, 95% CI −5.70 to −0.75; LCZ696 400 mg versus valsartan 320 mg,−5.14 mm Hg, 95% CI −7.70 to −2.59).

However, there was no significant treatment difference in maDBP reductions, thereby providing evidence of improvements in PP with LCZ696 versus valsartan. These findings are consistent with improvements in large artery function. Furthermore, BP control rates were significantly higher with LCZ696 200 mg than with 160 mg valsartan (46% [78/168] versus 33% [54/163], p = 0·0147). Importantly, in these studies, unlike the vasopeptidase inhibitor omapatrilat, LCZ696 was generally well tolerated without an incidence of angio-oedema during 8 weeks of treatment.[21]

The reported improvements in PP suggest the potential for LCZ696 to protect more effectively than the existing BP-lowering agents from several consequences of ISH and vascular stiffness, such as stroke and diastolic heart failure. However, in the study by Ruilope et al[21] CAP, central haemodynamics and arterial stiffness were not assessed, precluding a meticulous assessment of the mechanisms underpinning the superior antihypertensive properties of LCZ696.

In the PARAMETER study, the measurement of CAP should more accurately assess the loading conditions on the LV, myocardium, coronary arteries, cerebral vasculature, and therefore theoretically CAP should provide a basis for more effective protection against CV target organ damage and events compared with brachial pressures. In this regard, even in normotensive individuals, measurement of aortic BP enhances the ability to predict the target organ changes.[44]

The PARAMETER study was initiated in December 2012 with a novel design to evaluate central haemodynamics in elderly patients with ISH and a widened PP at 12 and 52 weeks of treatment with LCZ696 or ARB olmesartan. If the changes in CASP at 12 weeks (acute haemodynamic effect) are larger than that in SBP, this would support the hypothesis that LCZ696 has the potential to favourably impact aortic haemodynamics and improve ventricular-vascular coupling in elderly patients with aged aortas and ISH. Treatment differences in PWV at 52 weeks would further support a direct beneficial effect of LCZ696 on aortic stiffness due to structural changes, independent of MAP, as both treatment groups will be titrated to achieve similar BP control. The overall effect of LCZ696 on maBP (maSBP, maDBP and maPP), 24-hour BP variability (standard deviation, covariance), and circadian BP rhythms (nocturnal dipping status and morning surge) will also be assessed in

comparison with olmesartan. The study targets randomisation of 432 patients and final results are expected in 2015. W~~Although w~~e acknowledge the limitations of this ~~such a~~ study which is designed to look at surrogate markers rather than major cardiovascular outcomes, ~~and not at major CV clinical outcomes~~ nevertheless, this is important to establish if there are differential effects of drugs therapies on surrogate outcomes of cardiovascular disease to justify and impact on the design of subsequent phase III studies assessing the potential of LCZ696 for enhanced cardiovascular disease and stroke prevention in elderly patients with ISH. ~~we believe that tThe results of the PARAMETER study, which investigates the effect of two treatment strategies on CAP and aortic stiffness which are predictors of the CV risk will impact the design of phase III studies assessing the CV protection potential of LCZ696 in elderly patients with ISH.~~

In addition to the PARAMETER study, the efficacy and safety of LCZ696 is being evaluated in related studies, for example, in comparison with olmesartan in elderly patients with mild-to-moderate hypertension, in patients with systolic hypertension and in patients with systolic hypertension who did not respond to olmesartan. Although it is hypothesised in the PARAMETER study that LCZ696 will be more effective at lowering both central aortic and brachial BP compared with olmesartan, it is also recognised that other agents may need to be added to reach recommended BP goals in the elderly patients with systolic hypertension. Both calcium channel blockers (CCBs, usually amlodipine) and diuretics are the most commonly used antihypertensive agents in combination with RAAS blockade for patients failing to achieve their BP goal with RAAS blockade monotherapy. Besides being very effective, such combination therapies of specific antihypertensive classes may also improve safety and tolerability. For example, addition of ARBs to CCBs has been shown to reduce the peripheral oedema associated with amlodipine monotherapy.[45] Similarly, diuretic-induced hypokalaemia has been shown to be attenuated when RAAS blockade is combined with diuretic therapy.[46] To further evaluate such combination therapies with LCZ696, the BP-lowering efficacy, safety and tolerability is being evaluated in combination with amlodipine in patients with mild-to-moderate hypertension who were non-responsive to amlodipine and in patients with systolic hypertension. There are also other trials investigating the efficacy and safety of LCZ696 in patients with severe hypertension and in patients with renal impairment.

In summary, the PARAMETER study will evaluate mechanisms associated with BP-lowering in elderly patients with an aged CV system as evidenced by systolic hypertension and a widened PP. The study will define whether LCZ696, a first-in-class ARNI is more effective in lowering CASP and CAPP than the ARB olmesartan and also explore whether this effect is related to a BP-independent reduction in arterial stiffening, suggesting a novel mechanism to target systolic hypertension, a major and increasingly important unmet therapeutic need in the management of hypertension in elderly patients.

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CONFLICTS OF INTERESTS

BW, JC, and KK have received honoraria from Novartis for consulting and presentations at scientific symposia. DZ, PC, AH, PB, and JZ are employees of Novartis and are thus eligible for Novartis stock and stock options.

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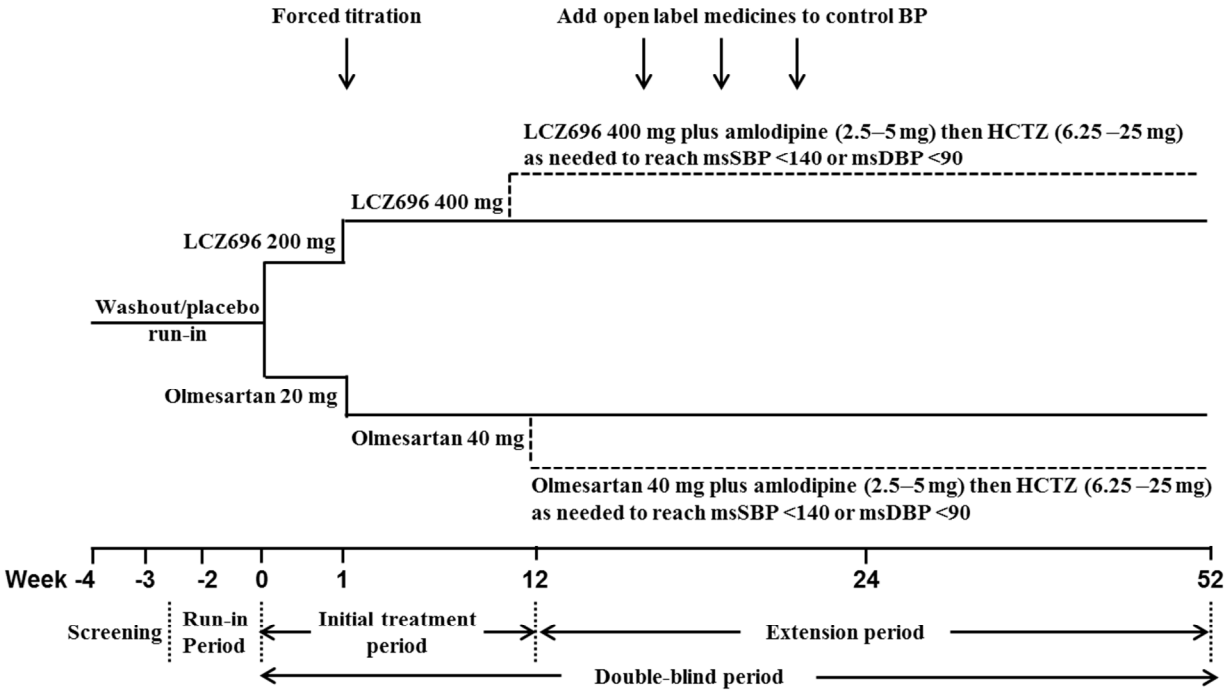
Figure 1. Study design



HCTZ, hydrochlorothiazide; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure

Box 1.

Inclusion criteria

- Patients with essential hypertension aged ≥60 years
- Either untreated or treated with antihypertensive agents, and who have msSBP ≥150 and <180 mm Hg at randomisation are eligible to be included.
    - Untreated patients (if they are newly diagnosed or have not been treated with antihypertensive drugs for the 4 weeks prior to screening) must have msSBP ≥150 mm Hg and <180 mm Hg at screening and randomisation.
    - Patients who have been treated with antihypertensive drugs during 4 weeks prior to screening must have msSBP ≥140 mm Hg and <180 mm Hg after 1 or 2 weeks of washout/placebo run-in and ≥150 mm Hg and <180 mm Hg at randomisation.
    - Patients must have a difference in msSBP of within ±15 mm Hg between randomisation and the visit preceding randomisation.
- All patients must have a PP>60 mmHg at randomisation.
- Patients who comply with all study requirements and demonstrate good medication compliance (≥80% compliance rate) during the amlodipine run-in period

Box 2.

Exclusion criteria

- Malignant or severe hypertension or secondary causes of hypertension
- History of atrial fibrillation or atrial flutter during 3 months prior to screening or active atrial fibrillation or atrial flutter on electrocardiogram during 12 months prior to screening
- History of cardiovascular disease (e.g., myocardial infarction) during the 12 months prior to screening
- Existing angina pectoris requiring pharmacological therapy (other than patients on a stable dose of oral or topical nitrates)
- Type 1 or type 2 diabetes mellitus not well controlled based on the investigator's clinical judgment
- Previous or current diagnosis of heart failure (NYHA Class II-IV), cardiac abnormalities such as Second or third degree atrioventricular block without a pacemaker, or malignancy
- Evidence of severe renal impairment (e.g., estimated glomerular filtration rate [eGFR] <30 ml/min//1.73 m^2
- Laboratory abnormalities such as serum potassium >5.5 mmol/L
- Known active liver disease or cirrhosis or evidence of hepatic disease
- Patients requiring any drug treatment that could affect BP
- Women of child bearing potential unless using highly effective methods of contraception during dosing

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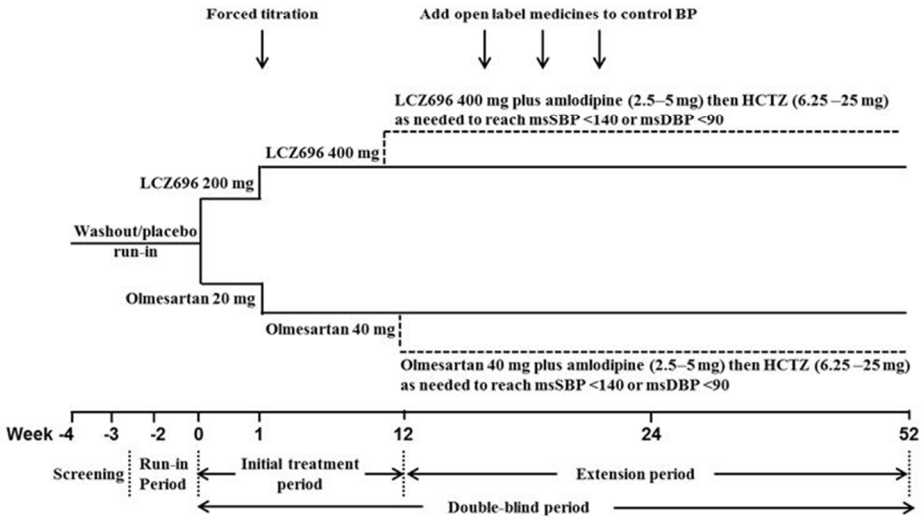
Figure 1. Study design



HCTZ, hydrochlorothiazide; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure

211x169mm (96 x 96 DPI)